Anesthesia of wood bison with medetomidine-zolazepam/tiletamine and xylazine-zolazepam/tiletamine combinations

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Abstract — This study was designed to evaluate 2 combinations for immobilization of bison. Seven wood bison received 1.5 mg/kg body weight (BW) of xylazine HCl + 1.5 mg/kg BW of zolazepam HCl and 1.5 mg/kg BW of tiletamine HCl on one occasion. The bison received 60 µg/kg BW of medetomidine HCl + 0.6 mg/kg BW of zolazepam HCl and 0.6 mg/kg BW of tiletamine HCL on another occasion. Xylazine was antagonized with 3 mg/kg BW of tolazoline HCl and medetomidine HCl was antagonized with 180 µg/kg (BW) of atipamezole HCl. Temporal characteristics of immobilization and physiological effects (acid-base status, thermoregulatory, cardiovascular, and respiratory effects) of the drug combinations were compared. Induction was significantly faster with xylazine HCl-zolazepam HCl/tiletamine HCl. Recovery following antagonist administration was significantly faster with medetomidine HCl-zolazepam HCl/tiletamine HCl. The average drug volumes required were 7.00 mL of xylazine HCl-zolazepam HCl/tiletamine HCL and 2.78 mL of medetomidine HCl-zolazepam HCl/tiletamine HCl. Hypoxemia, hypercarbia, and rumenal tympany were the major adverse effects with both drug combinations.

Résumé — **Anesthésie du bison des bois avec les associations médétomidine-zolazépam / tilétamine et xylazine-zolazépam / tilétamine.** Cette étude était conçue pour évaluer 2 associations destinées à immobiliser les bisons. Sept bisons des bois ont reçu en une occasion 1.5 mg/kg de poids corporel (PC) de chlorure de xylazine ainsi que 1.5 mg/kg PC de chlorure de zolazépam et 1.5 mg/kg PC de chlorure de tilétamine. À une autre occasion, les bisons ont reçus 60 µg/kg PC ainsi que 0.6 mg/kg PC de chlorure de zolazépam et 0.6 mg/kg PC de chlorure de tilétamine. La xylazine a été antagonisée par 3 mg/kg PC de chlorure de tolazoline et le médétomidine par 180 µg/kg PC de chlorure d'atipamézole. Les caractéristiques chronologiques de l'immobilisation et les effets physiologiques (équilibre acide-base, thermorégulation, effets cardiovasculaires et respiratoires) des associations médicamenteuses ont été comparées. L'induction était significativement plus rapide avec les chlorures de xylazine, zolazépam et tilétamine. La période de recouvrement suite à l'administration d'antagonistes était significativement plus rapide avec les chlorures de médétomidine, zolazépam et tilétamine. Le volume moyen des injections était de 7 mL pour les associations de chlorures de xylazine, zolazépam et tilétamine et de 2,78 mL pour ceux de médétomidine, zolazépam et tilétamine. L'hypoxémie, l'hypercapnie et le tympanisme du rumen ont été les effets indésirables les plus graves remarqués avec les deux associations médicamenteuses.

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Introduction

Bison are becoming increasingly popular as a game-farmed species. Bison may require immobilization for

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a variety of reasons, including dystocia, capture of escaped animals, and medical or surgical interventions. Historically, muscle relaxant drugs, such as succinylcholine, were used to produce immobilization (1). Concerns about the humaneness of this treatment and a low therapeutic index limit the acceptability of this drug. Potent narcotics, such as carfentanil, have been used in combination with xylazine HCl to produce effective immobilization of free-ranging bison (2,3), but many wildlife managers and veterinarians are unwilling to use these drugs because of safety concerns. Currently, there are no safe, reliable drug combinations available for anesthetizing bison.

The following paper details results of a study designed to determine the efficacy and physiological effects of 2

potentially useful combinations. Medetomidine HCl-zolazepam HCl/tiletamine HCl is a potent, reversible combination that has been used effectively in polar bears *(Ursus maratimus)* (4), black bears *(Ursus americanus)* (5), and a variety of nondomestic hoof stock and carnivores (6). Xylazine HCl-zolazepam HCl/tiletamine HCl is also reversible, and has been used successfully in wapiti (7).

Materials and methods

This study was performed during February 1998 in Elk Island National Park, Alberta. The study design was approved by the University of Saskatchewan Animal Care Committee. Seven male wood bison, ranging in age from 3 to 5 y, and body mass from 386 to 462 kg, were anesthetized. They were fasted for at least 24 h prior to drug injection. Each bison received both combinations in random order, determined by coin toss. The treatments were administered 1 wk apart to allow for drug metabolism and excretion. Drug doses were extrapolated from doses used in other ungulates (6) and from the authors' experience with these combinations in plains bison and other ungulates. The drug solutions were prepared as follows: (1) 2.5 mL of xylazine HCl (Rompun, Bayer Etobicoke, Ontario) was added to 500 mg of zolazepam HCl/ tiletamine HCl (Telazol, Fort Dodge Laboratories, Fort Dodge, Iowa, USA) (XZT). The mixed solution had a volume of 2.8 mL and contained approximately 89 mg/mL of xylazine and 178 mg/mL of zolazepam HCl/tiletamine HCl; and (2) 2.5 mL of 10 mg/mL medetomidine (Farmos Group, Turku, Finland) solution was added to 500 mg of zolazepam HCl/tiletamine HCl (MZT). The mixed solution contained approximately 8.9 mg/mL of medetomidine and 178 mg/mL of zolazepam HCl/tiletamine HCl.

Each bison was directed into a hydraulic chute and was weighed by electronic load scale (Senstek, Norac Systems, Saskatoon, Saskatchewan). The anesthetic combination was then injected by hand into the gluteal muscle mass. The XZT combination was administered intramuscularly (IM) as 1.5 mg/kg BW of xylazine HCl + 3 mg/kg BW of zolazepam HCl/tiletamine HCl. The MZT combination was administered IM as 60 μg/kg BW of medetomidine + 1.2 mg/kg BW of zolazepam HCl/tiletamine HCl. After being injected, the bison were released from the chute and moved into a holding pen.

The times from injection to sternal recumbency and head down were recorded. Immobilized bison were positioned in right or left lateral recumbency. The position was alternated between treatments in each bison. A 20-gauge, 5-cm catheter (Surflo, Terumo Medical, Irvine, California, USA) was placed in the saphenous artery for pressure measurement and arterial blood sampling. The catheter was connected with noncompliant tubing to a pressure transducer (Uniflow, Baxter Healthcare, Irvine, California, USA). The transducer was connected to a physiological monitor (Propaq 400 EL, Protocol Systems, Beaverton, Oregon, USA). Electrocardiograph leads were placed in a 3-lead axis, and lead II was constantly monitored. Body temperature was measured rectally with a digital thermometer. Heart rate (HR) was determined from the arterial pressure tracing, respiratory rate (RR), body temperature (temp), and mean

arterial pressure (MAP) were recorded every 5 min. A blood gas analyzer (AVL OPTI 1, AVL Scientific, Roswell, Georgia, USA) was used to measure $PaCO_2$, PaO_2, pH, and base excess (BE). Arterial blood samples were collected at 15, 30, 45, and 60 min postinjection. Blood gas samples were stored on ice and analyzed within 3 h of collection. Samples were corrected for hemoglobin concentration and body temperature.

At 60 min postinjection, the equipment was removed from the animal and $α_2$-antagonists were administered. Atipamezole HCl (Farmos Group) was administered at a dose of 90 μg/kg BW intravenously (IV), plus 90 μg/kg BW, IM, to antagonize medetomidine. Atipamezole was administered at 3 times the medetomidine dose, based on dosages reported to antagonize medetomidine in wild ruminants (8). Tolazoline HCl (Tolazine, Lloyd Labs, Shenandoah, Iowa, USA) was administered at a dose of 1.5 mg/kg BW, IV, and 1.5 mg/kg BW, IM, to antagonize xylazine. The tolazoline dose was based on dosages reported to antagonize xylazine-induced sedation in white-tailed deer (9) and on clinical experience with the drug in bison, elk and other ungulates (unpublished observations). The times from antagonist administration to sternal recumbency and standing were recorded.

Immobilization characteristics were compared with a paired *t*-test. Two-way analysis of variance (ANOVA) for repeated measures was used to compare physiological responses between treatments. One-way ANOVA for repeated measures was used to compare physiological parameters over time. Bonferroni correction for multiple comparisons was used to determine where differences occurred (10). The significance level for this study was $P < 0.05$.
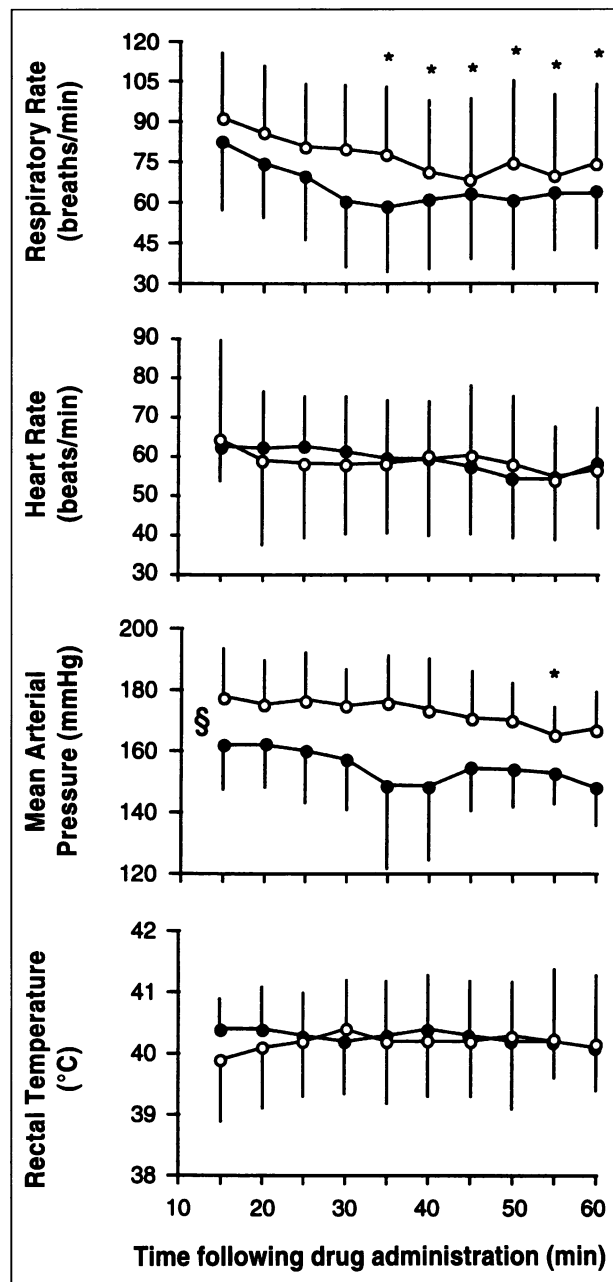
Results

Respiratory rate was rapid with both combinations, more so with MZT (Figure 1). The respiratory rate did not change significantly over time. The HR was not significantly different between treatments and did not change significantly over time. The MAP was significantly lower with XZT and did not change over time with either treatment. Rectal temperature was not significantly different between treatments and did not change over time. The arterial pH did not differ significantly between treatments and increased significantly over time with both treatments (Figure 2). With both treatments, the pH was significantly lower at 15 min compared with all other times. The pH at 30 min was significantly lower than at both 45 and 60 min. Both treatments produced some hypoventilation, as evidenced by an increased $PaCO_2$. The $PaCO_2$ was significantly greater with the XZT compared with the MZT. The $PaCO_2$ did not change significantly over time with XZT, but increased significantly over time with MZT. The $PaCO_2$ was significantly greater at 60 min postinjection (PI) of immobilizing agents compared with the reading at 15 min during the MZT immobilization. Both combinations produced hypoxemia ($PaO_2 < 60$ mmHg); this increased in severity over time. With both treatments the PaO_2 at 45 min PI was significantly lower than the PaO_2 at 15 min PI (Figure 2). The BE was not significantly different
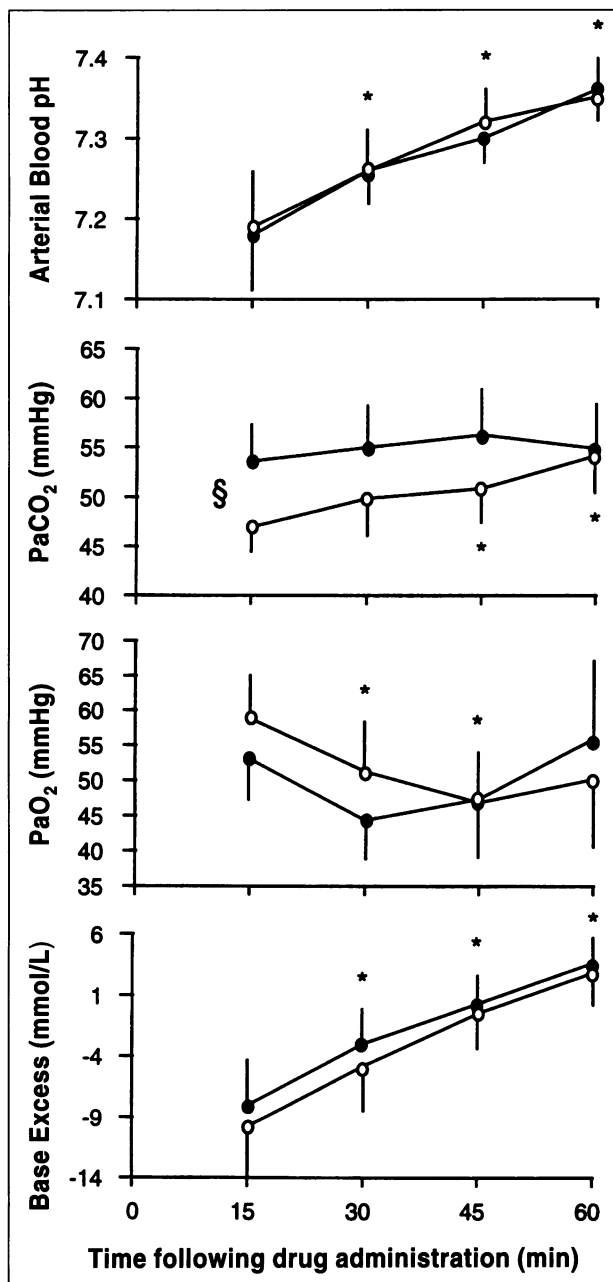
Figure 1. Comparison of physiological responses of 7 subadult wood bison during anesthesia with medetomidine HCl-zolazepam HCl/tiletamine HCl (MZT), and during anesthesia with xylazine HCl-zolazepam HCl/tiletamine HCl (XZT). Means and standard deviation bars are presented for wood bison anesthetized with MZT (O), and with XZT (●). Significant differences ($P < 0.05$) between response at 15 min and response at subsequent times are indicated by (*). Significant differences between drug treatments indicated by (§).

Figure 2. Comparison of blood gas responses of 7 subadult wood bison during anesthesia with medetomidine HCl-zolazepam HCl/tiletamine HCl (MZT), and during anesthesia with xylazine HCl-zolazepam HCl/tiletamine HCl (XZT). Means and standard deviation bars are presented for wood bison anesthetized with MZT (O), and with XZT (●). Significant differences ($P < 0.05$) between response at 15 min and response at subsequent times are indicated by (*). Significant differences between drug treatments indicated by (§).

between treatments and increased significantly over time with both treatments. With both treatments, BE was significantly lower at 15 min PI compared with BE measured at all other times; the BE at 30 min PI was significantly less than the BE at 45 and 60 min PI, and the BE at 45 min PI was significantly less than the BE at 60 min PI. Induction was significantly faster with the XZT combination, and recovery was significantly faster with the MZT combination (Table 1). The average drug

volume used was 7.00 mL with XZT and 2.78 mL with MZT. Immobilization was characterized by lack of spontaneous movement and lack of response to instrumentation. The XZT combination appeared to have a shorter duration of effects, as some animals were able to move their ears and limbs at 55 min PI. Mild rumenal tympany occurred with both treatments. One animal regurgitated 16 min post reversal with tolazoline. The animal was still recumbent at the time of regurgitation.

Table 1. Comparative immobilization features of medetomidine HC1-zolazepam HCl/tiletamine HC1 (MZT) anesthesia with atipamezole reversal, and xylazine HC1-zolazepam HCl/tiletamine HC1 (XZT) anesthesia with tolazoline reversal, in wood bison ($n = 7$)

Feature (min)	MZT + Atipamezole	XZT + Tolazoline	Statistical Significance[a]
Induction to sternal recumbency	7.5 (2.11)	4.1 (0.97)	*
Induction to head down	8.8 (2.10)	5.5 (1.08)	*
Antagonist administration to sternal recumbency	1.6 (0.94)	5.6 (3.05)	*
Antagonist administration to standing	1.7 (0.82)	11.8 (9.65)	*

[a]Paired t-test used to compare immobilization data of $n = 7$ wood bison
*Statistical significance at $P < 0.05$
Data shown as mean time ($s_{\bar{x}}$) it took to display the feature

Discussion

Both of these combinations are effective for immobilizing bison; however, hypoxemia is a significant concern. Hypoxemia is common in ruminants anesthetized with medetomidine-based drug combinations (11–14). Similarly, hypoxemia has been reported during xylazine sedation and anesthesia in ruminants (15). Other factors that may have contributed to hypoxemia include restraining the bison in lateral recumbency and the development of rumenal tympany. Sternal recumbency is a preferable position and should result in less hypoxemia (15). Hypoventilation, as evidenced by increased $PaCO_2$, was more severe with the XZT combination. In domestic sheep both medetomidine and xylazine produced decreased PaO_2, but neither drug produced an increase in $PaCO_2$ (hypoventilation) (16). Tiletamine-zolazepam has been shown to produce hypoventilation in sheep (17). The XZT combination requires approximately 3 times the dose of tiletamine-zolazepam compared with the MZT combination. It is possible that the increased $PaCO_2$ seen during XZT immobilization is a result of the higher dose of tiletamine-zolazepam. Hypoventilation was not severe ($PaCO_2$ remained < 60 mmHg) and, although hypoventilation would have contributed to hypoxemia, the major cause of hypoxemia was probably ventilation-perfusion mismatch.

Both xylazine and medetomidine have been shown to produce hypoxemia, mediated by increased venous admixture (16). Venous admixture is a calculated amount that is a proportion of cardiac output and includes the PaO_2-lowering effect of low V/Q areas of the lung (areas with adequate perfusion but poor ventilation), blood past nonventilated areas of the lung, and true shunt flow (18). The net effect of increased venous admixture is to lower PaO_2, with little effect on $PaCO_2$. Increased venous admixture has been measured in sheep anesthetized with medetomidine-ketamine (11). In medetomidine-ketamine anesthetized sheep, venous admixture (shunt flow) increased to a maximum of 24%. Supplemental inspired oxygen becomes less effective at increasing PaO_2 as shunt flow approaches 30% (18). Given the facts that supplemental inspired oxygen should tend to offset some of the decreased PaO_2 resulting from hypoventilation, and that supplemental inspired oxygen should help to improve oxygenation if shunt flow is < 30%, animals receiving these combinations should receive supplemental inspired oxygen. Since lateral or dorsal recumbency has been shown to decrease PaO_2 in ruminants (15), the animal should be maintained, when possible, in sternal recumbency, to decrease ventilation-perfusion mismatch and facilitate oxygenation. Further studies are recommended to determine the efficacy of supplemental inspired oxygen with these combinations.

Blood pressure was significantly higher with MZT. Medetomidine is a more potent and selective α_2-receptor agonist than is xylazine (19). The increased blood pressure is likely the result of peripheral α_2-receptor activation (11,19,20). Hypertension is commonly encountered during ruminant anesthesia (21). Calves anesthetized with XZT demonstrated mean arterial pressures comparable with those encountered in the current study (21). It is difficult to determine if the hypertension in the current study could be dangerous to the animal, but it would be advisable to use these combination drugs cautiously in animals with cardiopulmonary, renal, or hepatic disease. Without baseline measurements, it is difficult to comment on the heart rates encountered with these drug combinations. The mean heart rates observed during immobilization with MZT and XZT were slightly lower than the mean heart rate of 74.8 beats/min reported during immobilization with carfentanil-xylazine (3). The lower heart rates reported during the current study are probably related to the high dose of α_2-agonist used in the combinations. Calves anesthetized with XZT demonstrated a significant drop in heart rate attributable to xylazine. In calves, it was speculated that the decrease in heart rate was attributable to enhanced baroreceptor activity and, possibly, direct or indirect increase in vagal tone with a decrease in sympathetic tone (21). The BE and the pH were both low in the early stages of immobilization, likely as a result of increased muscular activity and anaerobic metabolism prior to immobilization. The animals were agitated at being handled and restrained in the chute. Metabolic acidosis has been observed in bighorn sheep following pursuit and capture (22), it has also been reported in racing greyhounds immediately following a race (23). The BE and the pH improved over time, possibly as a result of decreased activity. There was no respiratory compensation over time; in fact, the animals were experiencing a respiratory acidosis from the increase in $PaCO_2$. The mean temperature over time was 40.2°C with MZT and 40.3°C with XZT. This is probably a slight increase in temperature for this species and may reflect increased activity and stress during handling, prior to immobilization. Kock and Berger (3) reported a mean

rectal temperature of 38.6°C in bison that were captured with 1 dose of carfentanil-xylazine. Bison that required 2 or more doses of carfentanil-xylazine had significantly higher mean rectal temperatures, with a mean value of 39.6°C. The increased temperature was probably the result of increased pursuit times.

Rumenal tympany was never severe, nor was regurgitation a major problem. One of the animals in the study did regurgitate a small amount of rumen contents during recovery from XZT-induced immobilization. It is important to note that the study animals were fasted and, in an unfasted animal, both of these complications have the potential to be more severe.

Physical characteristics of immobilization suggest that XZT may be of more use for immobilization of game-farmed or captive animals than for immobilization of free-ranging bison. By using the described formulation, XZT is delivered at a relatively high volume; this necessitates the use of large, less accurate, darts. Recovery is also more prolonged with XZT, compared with MZT, this would not be a serious problem in a confined animal, but free-ranging animals may be at increased risk of predation. Recovery may be more prolonged for 2 reasons: 1) A higher dose of tiletamine HCl/zolazepam HCl is required in the XZT combination; this will result in more residual effects of the tiletamine HCl/zolazepam HCl following antagonism of the xylazine HCl with tolazoline HCl; and 2) Atipamezole HCl is a more selective α_2-antagonist drug than tolazoline HCl (24). It is quite possible that antagonism of the xylazine-induced sedation could be more complete with atipamezole HCl, and recovery may be less prolonged. The MZT combination can be delivered in a low volume, and induction time is significantly slower with than with XZT but should still be suitable for most situations. Recovery is significantly quicker with it than with XZT. Although induction time with MZT is significantly slower than with XZT, it is still comparable with induction times reported for carfentanil-xylazine. Haigh and Gates (1) reported an induction time of 6.4 ($s_{\bar{x}} = 0.4$) min following good dart placement. Kock and Berger (2) reported an induction time of 14.2 ($s_{\bar{x}} = 2.9$) min in plains bison. Small volume and rapid recovery make MZT more attractive for free-ranging animals. The animals used in this study were free-ranging animals that were acutely confined for the purpose of this study and were unaccustomed to handling. Induction time may be shorter in game-farmed animals that are more accustomed to human manipulation.

Antagonists were administered half IV and half IM. Several animals experienced full recoveries from MZT-induced sedation in less than 1 min. Atipamezole is active following IM injection (8), and IV administration is probably not advisable, unless a safe location can be reached in less than 1 min.

Acknowledgments

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